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Highly trained female athletes may experience loss of menses, low bone mass, and an increased frequency of stress fractures because of their participation in intense physical activity. Low serum estrogen levels are believed to be a principal cause of the bone loss. If so, re-establishing normal estrogen levels in these women should prevent or retard bone loss and decrease the incidence of stress fractures. This study is a two-year randomized trial of the effects of oral contraceptives on bone mass and stress fracture incidence among 150 female competitive distance runners in the age range 18-25 years. The Coordinating Center is at Stanford University and bone mass in being measured at five sites: Massachusetts General Hospital, University of California Los Angeles, University of Michigan, Stanford University/Palo Alto VA Medical Center, and Helen Hayes Hospital in West Haverstraw NY. Athletes are currently being recruited from the areas around these five clinical sites, and to date 84 have been randomized. Results will not be available until 2002.

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(5) INTRODUCTION

Highly trained female athletes may experience loss of menses because of their participation in intense physical activity. Previous cross-sectional research has shown that women with exercise-induced irregularities have a significantly higher frequency of stress fractures and low bone mass than normally menstruating controls. Longitudinal studies suggest that these women are losing bone mass over time. Low serum estrogen levels are believed to be a principal cause of the bone loss. If so, re-establishing normal estrogen levels in these women should prevent or retard bone loss and decrease the incidence of stress fracture. This study is a two-year randomized trial of the effect of oral contraceptives on bone mass and stress fracture incidence among 150 female cross country runners in the age range 18-25 years. The Coordinating Center is at Stanford University and bone mass is being measured at five sites: the Massachusetts General Hospital, the University of California Los Angeles, the University of Michigan, Stanford University/Palo Alto VA Medical Center, and the Helen Hayes Hospital in West Haverstraw, NY. Athletes are being recruited from the areas around these five clinical sites.

(6) BODY

Below we summarize (a) the progress that was made through year 2, (b) the status of recruitment as of the end of year 2, (c) our plans for reaching our goal of 150 athletes, and (d) the current status of the follow-up data collection. *At the end of sections (c) and (d), we report in italics the progress that has been made in the first four months of the third year of this grant, as this has bearing on the issues raised in the Review of the Annual Report.*

(a) Progress through through year 2 (excluding recruitment, which will be described under [b] below): During the first year of the study the following accomplishments were reported: The study has been introduced to coaches, athletes, student health services, and IRBs at many colleges, and procedures have been implemented to work with these individuals and groups. Informational packets have been developed and sent to coaches, athletes, student health services, and others. Informed consent forms have been developed and administered. Annual questionnaires, daily diaries, and six-month questionnaires have been developed, pilot tested, and, in the case of the baseline questionnaire and daily diaries, used for data collection. Data entry programs have been written and successfully used. A manual for the clinical sites has been written and implemented. The Project Director (Kristin Cobb) has spoken to athletes at many colleges and recently has begun to make the study known to athletes at high-profile races in the Stanford area. A randomization scheme has been developed and implemented. Oral contraceptives have been procured from Wyeth-Ayerst and procedures established for sending them to student health services and tracking them. Procedures have been set up with the study's medical monitor. Preliminary statistical analysis of the baseline data has been undertaken on the first 25 participants. Of all these tasks, by far the most time has been spent on working with so many different IRBs (many of which meet only a few times a year) and on recruitment.

During the second year of the study, athletes recruited during the first year have been followed, additional runners have been recruited, and the Army and Helen Hayes Hospital IRBs have finally agreed upon a mutually agreeable consent form. Negotiations with the Army and UCLA IRBs regarding the UCLA informed consent form for non-collegiate runners have been on-going for several months.

During the first year, recruitment was our biggest problem. Now that we have revised our recruitment methods and expanded the scope of the study eligibility to include non-collegiate highly competitive runners in the age range 18-25 years, we believe that we can recruit the target number of 150 participants. Our main problem at present is the length of time it takes to work out wording of the informed consent form that is mutually agreeable to the Army IRB and the IRBs at our clinical sites.

(b) Recruitment through year 2: The focus of our recruitment efforts in the second year of the study shifted from collegiate to non-student athletes. At the end of the first year of the study, 35 collegiate athletes had been randomized. During the second year, 14 additional collegiate athletes and 35 non-student athletes from the Stanford area were randomized for a total of 84.

Of the 14 additional collegiate athletes, 8 were athletes who had expressed interest in the study during the first year but who were delayed in attending their clinical visits; the other 6 were freshmen in the fall of 1999. These freshmen were recruited through the coaches of participating teams, who were asked to distribute informational packets about the study to new team members. Distribution of these packets was followed by an e-mail from the Project Director to all incoming freshman on teams where team rosters and student e-mail directories were available on the internet.

In November of 1999, we received Army IRB approval to recruit non-student highly competitive runners aged 18-25 in the Stanford area. Thirty-five non-student runners in the Stanford area were recruited through post-collegiate running clubs and area road races.

Members of post-collegiate running clubs were recruited through running web-sites, e-mail distribution lists, and club newsletters. Interested runners were instructed to contact the

study by telephone or e-mail to receive a more complete informational packet in the mail. This was followed by an e-mail or telephone call from the Project Director to determine interest and eligibility. This resulted in 4 new subjects.

Road race participants were recruited directly through advertisements and race-exposition booths at road race and track events in the Stanford area; this resulted in the recruitment of 3 new subjects. Road race participants were also recruited from race results. The results from road races in the Stanford Area taking place from January to June 1999 were obtained; address and phone information for females aged 18-25 years was located through race-directors, the internet, or telephone information. Runners were either sent an informational packet in the mail or were called by the Project Director and invited to participate in the study. This resulted in 5 new subjects.

By far the most successful recruitment strategy was mass mailings. Road race participants from the Stanford area were recruited from mail distribution lists compiled by *The Competitor* magazine. Flyers were mailed to 2000 female road-race participants whose mailing addresses were within a 60 mile radius of Stanford, who were aged 18-25, and who ran under 8-minutes per mile in their most recent race. Interested runners were instructed to contact the study by telephone or e-mail. Nineteen athletes were recruited through this approach; a follow-up mailing to those athletes in a smaller geographic radius resulted in 4 additional athletes.

(c) Further recruitment efforts to reach our goal of 150 athletes:

(1) In August of 2000, after 14 months of negotiation, we received army IRB approval to begin seeing runners at the Helen Hayes Hospital. Flyers were subsequently mailed to 2700 female runners aged 18-25 in the surrounding area. So far, 61 athletes have called or e-

mailed in response to these, 18 have been successfully screened, and 6 have scheduled their clinical appointments. Through this initial mailing, a subsequent follow-up mailing, and collegiate athletes who were recruited last year, we expect to enroll at least 30 runners total from New York.

(2) Packets have been mailed to coaches at 15 participating colleges for distribution to freshmen and new team members. Last year, 6 new freshman subjects were recruited in this manner. Thus, we expect about 6 to enroll again this year.

(3) We are awaiting Army IRB approval to begin to enter non-student athletes into the trial at the Los Angeles site. We expect that, once we have approval from the army IRB, within 2-3 months we will have an additional 40 randomized participants.

(4) With the help of our Project Officer Lieutenant Colonel Sheehan, we have obtained permission to recruit athletes from West Point to augment our numbers further.

As mentioned above, in August 2000 we received Army IRB approval to recruit runners to be seen at the Helen Hayes Hospital in West Haverstraw, NY. In October of 2000 and January of 2001, flyers were mailed to over 2500 female road-race participants whose mailing addresses were within an 80-mile radius of the Helen Hayes Hospital and who were 18-25 years of age. Runners were also recruited through an advertisement in Runner's World Magazine and mail distribution lists complied through Runner's World magazine. To date, 7 have been randomized, 4 have been successfully screened using the preliminary telephone interview, and several more from the January mailing are being screened.

From additional mass mailings in the Stanford area, 8 additional runners have been randomized or successfully screened. One more collegiate runner has also been enrolled. This brings us to a total of 104 runners who have been randomized or who are scheduled to be examined and randomized.

The other significant progress that has been made is that as of the first week in February, representatives of the Army and UCLA IRBs appear to have agreed on wording on the protocol and consent form for non-collegiate runners at that site. As best as we can tell, there are no remaining unresolved issues. We would expect that within about two months, the full IRBs of both the Army and ULCA will have approved the protocol.

We now are quite confident that we will be able to enroll 150 runners who meet the study criteria, and that we will be able to do this by the end of year 3. Our reasoning is that we have now recruited 43 non-collegiate runners from the Stanford area. Since we expect to receive IRB approval shortly to recruit non-collegiate runners from the Los Angeles area, since the same types of lists of road-race participants are available in that area as in the Stanford area, since the population of the Los Angeles area is much greater than in the Stanford/San Francisco area, and since the clinical examination and bone densitometry will take place at a location convenient to residents of Los Angeles, we should be able to recruit 40-50 participants within a 3-4 month period of obtaining final IRB approval. This, combined with some additional runners still being screened in the Stanford and New York areas, should put us over the target of 150 participants.

Assuming that we accomplish this, we would need to extend the period of funding for about two years beyond the originally planned project period of three and one half years. However, it does not appear that we will need additional money. We have spent considerably less than anticipated over the first two years of the project for several reasons. We are only charged for bone densitometry when it is done, so we still have money for the remaining bone measurements. We had to reimburse travel expenses of collegiate athletes who were sometimes travelling over 100 miles, and reimbursement for the non-collegiate runners who are travelling much shorter distances is less. Recruitment was poor at our most expensive site for bone densitometry, the University of Michigan, while the Helen Hayes Hospital and Stanford, which were added after the study started, are less expensive. The Principal Investigator reduced her reimbursed time commitment to 5% in order to save money, and she is not using money from this project to travel to scientific meetings. The time of the Associate Project Director is now at 80% instead of 100%, and some of her tasks (e.g., data entry) are being done by less expensive Stanford undergraduates. With all these money-saving efforts, we should be able to complete the data collection without the need for additional funds, but we will need additional time. Finally, the Principal Investigator, Project Director, and Biostatistician are committed to completing the data analysis and writing up the results even if funding has run out before these tasks have been completed.

Another option, as suggested in the Review of the Annual Report, is to expand the network of participating collegiate athletic departments and to focus on spontaneous presentation of women collegiate athletes with running-related bone injuries, their treatment, and follow-up. We believe that this is another important question, but it would be almost a new project, and could

not simply be added to what we have done already. Yet another option would be to expand the current protocol to other geographic areas, but this would not be financial feasible since we would have to set up new infrastructures for physicians to examine participants and prescribe oral contraceptives and for personnel to measure bone densitometry. Also, based on recent experience, we would anticipate that it would take an average of about a year to obtain IRB approvals to recruit at new sites.

Thus, we propose the following: Assuming that we do obtain IRB approval to recruit non-collegiate runners in the Los Angeles area, we suggest that we be given four months from that date to reach our target of 150. If we do not, then the study should be closed down. Given that the question that the study is addressing really does need to be answered, and given that we are now quite close to being able to enroll the required number of study subjects before the end of the third year, we hope that our reviewers will extend their patience for just a few more months.

(d) Follow-up data collection: At this time last year, 40 runners had been randomized. Thus, by now, 40 athletes should have completed their first-year follow-up visits. In fact 28 have completed 3 visits. Of the other 12, five only recently became due for their appointments and are in the process of scheduling, and 7 have been delayed in scheduling their appointments. Thus, we appear to be doing better than is suggested in the review. Frankly, we had no idea that collegiate athletes would be such "terrible study participants," but the non-collegiate runners who are just slightly older in chronological age than the collegiate runners have been much more responsible from the outset about making and keeping appointments and in general following instructions.

(7) KEY RESEARCH ACCOMPLISHMENTS: None to date.

(8) REPORTABLE OUTCOMES: None to date.

(9) CONCLUSIONS: We will have no conclusions to report until the end of the trial.

(10) REFERENCES: None

(11) APPENDICES: None